HSPI The Open Access Publisher

JNND JOURNAL OF NEUROSCIENCE AND NEUROLOGICAL DISORDERS
ISSN 2639-3220

Review Article

The Potential Use of Dimethyltryptamine against Ischemia-reperfusion Injury of the Brain

Attila Kovacs, Anna Mathe and Ede Frecska*

Department of Psychiatry, Faculty of Medicine, University of Debrecen, Hungary

Abstract

Ischemia-Reperfusion Injury (IRI) is the outcome of two intertwined pathological processes resulting from the shortage of blood flow to tissues and the subsequent restoration of circulation to a previously ischemic area. IRI (sometimes just one side of the dyad) remains one of the most challenging problems in several branches of emergency medicine. Mitochondrial and endoplasmic reticulum dysfunction is a crucial pathological factor involved in the development of IRI.

The sigma-1 receptor (Sig1-R) is an intracellular chaperone molecule located between the mitochondria and endoplasmic reticulum with an apparent physiological role in regulating signaling between these cell organelles and serves as a safety mechanism against cellular stress. Therefore, amelioration of IRI is reasonably expected by the activation of the Sig1-R chaperone. Indeed, under cellular stress, Sig1-R agonists improve mitochondrial respiration and optimize endoplasmic reticulum function by sustaining high-energy phosphate synthesis.

The discovery that N, N-dimethyltryptamine (DMT) is an endogenous agonist of the Sig1-R may shed light on yet undiscovered physiological mechanisms and therapeutic potentials of this controversial hallucinogenic compound. In this article, the authors briefly overview the function of Sig1-R in cellular bioenergetics with a focus on the processes involved in IRI and summarize the results of their *in vitro* and *in vivo* DMT studies aiming at mitigating IRI. The authors conclude that the effect of DMT may involve a universal role in cellular protective mechanisms suggesting therapeutic potentials against different components and types of IRIs emerging in local and generalized brain ischemia after stroke or cardiac arrest.

More Information

***Address for correspondence:** Ede Frecska, M.D., Ph.D., Clinical Director, Department of Psychiatry, Faculty of Medicine, University of Debrecen, Nagyerdei krt. 98., Debrecen, 4032, Hungary, Email: frecska.ede@med.unideb.hu

Submitted: March 28, 2024
Approved: April 18, 2024
Published: April 19, 2024

How to cite this article: Kovacs A, Mathe A, Frecska E. The Potential Use of Dimethyltryptamine against Ischemia-reperfusion Injury of the Brain. J Neurosci Neurol Disord. 2024; 8: 050-056.

DOI: 10.29328/journal.jnnd.1001097

Keywords: Brain ischemia; Dimethyltryptamine; Ischemia-reperfusion injury; Sigma-1 receptor; Stroke

Abbreviations: 5-HT: Serotonin; 5-MeO-DMT: 5-methoxy-N, N-dimethyltryptamine; ATP: Adenosine Triphosphate; DMT: N, N-Dimethyltryptamine; IL: Interleukin; IRI: Ischemia-Reperfusion Injury; MAM: Mitochondria-Associated Membranes; SD: Spreading Depolarization; Sig-1R: Sigma-1 Receptor; TNF: Tumor Necrosis Factor

Introduction

Ischemia-Reperfusion Injury (IRI) is a complex pathological issue that poses significant challenges in various medical fields, including cardiovascular surgery, stroke therapy, emergency medicine (particularly after a heart attack), cardiorespiratory resuscitation, neonatology, sepsis, and organ transplantation [1]. Ischemic injury refers to the condition evolving when a tissue area is cut short of blood flow, leading to a lack of oxygen and nutrients. This happens in stroke, myocardial infarction, and other thromboembolic events. Ischemic injury can also occur during surgery when arteries are cross-clamped and in organs intended for transplantation. In the end, prolonged deprivation of blood supply results in necrotic cell death.

Restoration of circulation is vital for tissue survival and mitigates the ischemic damage, but paradoxically it may cause extra harm known as reperfusion injury. This sequela is due to the activity of free radicals (i.e., reactive oxygen species of the oxidative stress) since the protective antioxidant mechanisms got compromised during the ischemic period. Eventually, oxidative stress leads to apoptotic cell death mediated by a cytokine storm. IRI is the term for the outcome of these combined pathological processes.

The sequence of events occurring in IRI

IRI is a phenomenon that involves multiple steps and factors in its pathomechanism [2,3]. Ischemia causes a deficiency of oxygen and nutrients, resulting in a decrease in oxidative metabolism, buildup of waste products, and depletion of high-energy phosphates. Among these, the core process is the decrease in cellular oxidative phosphorylation. Due to the insufficient oxygen supply the energy support of cellular homeostasis declines, since the mitochondrial respiration and consequently the endoplasmic reticulum machinery becomes deficient. Ischemia alters the equilibrium of ions since the decrease in high-energy phosphates leads to the dysfunction of ATP-dependent membrane ion pumps,

resulting in calcium, sodium, and water influx to the cells. Under special circumstances and for a limited period the cells adapt by utilizing anaerobic pathways. The accumulation of lactate caused by anaerobic metabolism leads to a drop in intracellular pH [4]. Ultimately, as a result of insufficient aerobic metabolism, the reserves of high-energy phosphates become exhausted leading to endoplasmic reticulum stress. Sustained perturbation of the endoplasmic reticulum results in prolonged unfolded protein response which triggers lethal cellular events. The membrane functions to break down, and the compartment-lesion of cellular organelles leads to necrotic cell death [5].

Once blood flow is reestablished, the aerobic metabolism restarts. An abrupt increase in oxygen delivery to the tissue can cause an accumulation of reactive oxygen species (such as hydrogen peroxide, superoxide, hydroxyl radical, and singlet oxygen) due to the stressed, overwhelmed antioxidant system. Oxidative cell damage occurs including lipid peroxidation. The initial stage of reperfusion injury is primarily characterized by the appearance of damage-associated molecular patterns. These elements trigger the inflammatory transcription factor NF-κB [6]. The subsequent release of pro-inflammatory cytokines, such as IL-1, IL-8, and TNF-α, add to the harm produced by reactive oxygen species and other free radicals during reperfusion. The induced inflammatory response involves the recruitment of immune cells, specifically neutrophils and macrophages, which then attack the reperfused tissue. Reperfusion promotes the entry of calcium into cells, with subsequent activation of several enzymes and adhesion factors that contribute to apoptosis [7].

The immune mechanisms and pathways involved in this process also encompass the disruption of glial cell functions in the brain, the entry of circulating peripheral leukocytes into both the central nervous system and peripheral tissues, and the overactivation of tissue-resident immune cells. The released cytokines exert systemic effects and cause distant damage to the lungs and other organs. Reperfusion injury can impair endothelial function, resulting in increased vascular permeability, leukocyte adhesion, and blood clot formation. These further compromise tissue perfusion and function. Reperfusion can increase the mitochondrial disfunction caused by ischemia, aggravate the impairment of cellular energy production, and intensify oxidative stress. The primary agents engaged in the detailed process include inflammatory cytokines and chemokines, adhesion factors, reactive oxygen species, and nitric oxide [8]. Most of the injury caused by ischemia-reperfusion occurs during the reperfusion phase and is mediated by the immune system [9]. In summary, tissue damage is determined primarily by the magnitude and duration of the ischemia, but in addition, a very significant injury develops during the subsequent reperfusion [2,3].

Therapeutic approaches against IRI

Due to its wide occurrence in different medical fields, IRI has become a common clinical concern, and its prevention or mitigation is an area of great clinical interest [4]. Strategies to reduce IRI include pre-conditioning the tissue to make it more resistant to the lack of oxygen, pharmacological methods targeting oxidative stress (by facilitation of free radical defense mechanisms, administering radical scavengers, metal chelators), inflammation (by administration of IL-1 receptor antagonist, soluble TNF-α receptors, antibodies against IL-1, TNF-α or adhesion molecules), and interventions aimed at preserving mitochondrial function. Additionally, techniques such as inducing hypothermia, gradual reperfusion, and remote ischemic conditioning have shown promise in reducing IRI in various clinical settings [10]. In organ transplantation many attempts have been made to reduce cold ischemia time, to develop better perfusion fluid, and to create a new perfusion technique [11]. Since IRI is damaged due to hypoxia and inflammatory cascade, a simple pharmacological intervention targeting both factors—each one on the ischemic or reperfusion side—may have clinically significant therapeutic potential. In this article, we demonstrate that activating the sigma-1 receptor (Sig-1R) with the external administration of one of its natural ligands, namely the endogenous hallucinogen N, N-dimethyltryptamine (DMT) offers a powerful tool against each component of IRI.

The Sig-1R chaperone

The Sig-1R molecule is an intracellular chaperone positioned in the Mitochondria-Associated Membranes (MAMs), which are placed between the endoplasmic reticulum and mitochondria. Its gene is expressed in many tissues, especially in the central nervous system [12]. The Sig-1R regulates Ca^{2+} signaling and serves a function in protecting against endoplasmic reticulum stress [13-15]. The conceptualization of Sig1-R as an important factor in protein maturation and modification is emerging [16], and points toward its involvement in the unfolded protein response. Normally, Sig-1R is in a less active state [17-19]. During extended cellular stress, the activation of Sig-1R moderates the pathways that lead to cell death by apoptosis [5]. The reduced activity of Sig-1R hampers the detection of endoplasmic reticulum stress prevents the activation of unfolded protein response, and consequently decreases cell survival by poorly interacting with the mitochondrion-endoplasmic reticulum-nucleus signaling mechanisms [20]. Sig-1R agonists improve mitochondrial function by preserving mitochondrial respiration, enhancing mitochondrial calcium uptake, and sustaining high-energy phosphate synthesis to optimize endoplasmic reticulum function [21-23].

The role of Sig-1R in cell survival

The activity of Sig-1R at the MAM helps cells survive by

regulating the influx of Ca^{2+} from the endoplasmic reticulum to the mitochondria. This process helps reduce endoplasmic reticulum stress. At the same time, it alleviates the harmful effects of free radicals through the Nrf2-antioxidant response element signaling [24,25]. Sig-1R agonists facilitate the translocation of this receptor from the MAM to the plasma membrane. The translocation of Sig-1R supports the regulation of many membrane-bound or cytosolic functional elements, for example, metabotropic receptors, ion channels, and protein kinases. Another translocation of Sig-1R from the MAM to the nucleus membrane provides interference with the transcriptional regulation of genes [26]. Possessing both chaperone and receptor function, and due to the versatility of its targets, the Sig-1R represents a pluripotent modulator in living systems and is involved in the etiopathology of many diseases [27-29].

The pharmacology of Sig-1R

Sig-1R has a unique and distinctive history. Initially, it was classified as a member of the opioid receptor family. Later on, it was considered to belong to the orphan receptor group [30] for which no endogenous ligand was known—until the discovery that DMT is its endogenous agonist [31]. Nowadays, Sig-1R is considered to be a non-G-protein coupled, nonionotropic intracellular chaperone [5]. Sig1-R is a well-established drug target [16]. With its pharmacological profile, Sig1-R represents a promiscuous receptor since it binds to ligands with very diverse structures. These include small molecules that also interact with other receptors, such as fluvoxamine, fluoxetine, dextromethorphan, methamphetamine, haloperidol, verapamil, donepezil, chloroquine, and more [32].

DMT as a natural Sig-1R ligand

DMT is a naturally occurring classical hallucinogen with significant affinity at 17 known receptor sites [33]. The discovery of DMT as a natural ligand of the Sig-1R [31] helped to clarify the decades-long perplexing history of both these molecules. DMT has been classified as an endogenous hallucinogen [34,35] with its exact physiological role unknown [36]. Nearly half a century of research was insufficient to offer a proper neurobiological explanation of the functions of this endogenous substance [37]. One reason for this is a paradigm issue, wherein the studies of DMT have mostly focused on its hallucinogenic effect mediated by the serotonin (5-HT1A, -2A, and -2C) receptors [38]. Moreover, DMT is a trace amine [39,40]. Trace amines are elusive; under normal conditions, they are present in the body in low concentrations, and it is not easy to determine the circumstances when they are mobilized. One noticeable fact is that there was a significant increase in DMT levels in the rat cortex following the induction of experimental cardiac arrest [41]. This supports our notion that DMT may play a role in the process of agony [42] when activation of Sig1-R can be beneficial, and data is available about its increased expression in different causes of death—particularly under hypoxic conditions [43]. We advise, that the conventional conceptualization of DMT as predominantly a serotonergic hallucinogen is too biased and limited in attributing to it solely a psychopathogenic function. In a previous paper [42] we emphasized that the Sig-1R action of DMT could provide valuable and relevant information regarding its potential physiological and clinical effects. DMT has a modest affinity for Sig-1R, with a K_D value of 14.8 μM [31]. This suggests that larger quantities of DMT are required to fully saturate the Sig-1R receptor compared to its lower K_D at the 5-HT receptor subtypes. Nevertheless, due to the co-localization of the DMT synthesizing indolethylamine N-methyltransferase enzyme and Sig-1R in neural tissue [44], it is possible that physiologically significant concentrations can be achieved at the Sig-1R site. No higher potency endogenous ligand for the Sig-1R has been identified yet, therefore DMT has been postulated as a noteworthy molecule [31,45].

Possible physiological and/or therapeutic roles of DMT

Since the Sig-1R alleviates endoplasmic reticulum stress [46], improves neuronal survival against oxidative stress [24], regulates immune processes [47], ameliorates IRI [48], induces autophagy [49-51], and provides neuroprotection [52,53], it is reasonable to ascribe a similar function to DMT [42]. Given that Sig-1R is recognized for its role in regulating the morphogenesis of neuronal cells, including processes like neurite outgrowth, myelination, and synaptogenesis; neuroregeneration [54] can plausibly be expected by its activation with DMT. In a study conducted by Dakic, et al. [55], it was found that in brain organoids 5-MeO-DMT (a compound closely related to DMT) positively influenced neuroplasticity and neuroprotection, maturation of dendritic spines, while inhibited factors involved in neurodegeneration and apoptosis. In a rodent model, DMT reduced reactive oxygen species production, inflammatory gene expression caused by predator exposure/psychosocial stress, and modulated neuroplasticity-related genes [56]. In our paper [42] we concluded that the function of DMT may involve a universal role in different tissue protective mechanisms—not solely brain-related. This theoretical paper was followed by experimental studies wherein the Sig-1R-mediated anti-inflammatory [57] and anti-hypoxia effects [58] of DMT were verified in vitro.

In vitro studies indicating Sig-1R mediated effect of DMT against inflammation and hypoxia

In our first experiment [57] we evaluated the effect of DMT, its derivative 5-MeO-DMT, and the synthetic Sig-1R agonist PRE-084 on inflamed human primary monocyte-derived dendritic cells. This was performed after inducing inflammation using lipopolysaccharide, polyI: C, or pathogen-derived stimuli. Our study revealed that administering these Sig-1R agonists suppressed the production of pro-

inflammatory cytokines, such as IL-1β, IL-6, IL-8, and TNF-α. Additionally, DMT application led to an increased secretion of the anti-inflammatory cytokine IL-10. The model also revealed a decrease in T-cell activation. The involvement of Sig-1R was verified using gene silencing.

In the second study [58] we examined whether activating Sig-1R by DMT can enhance the survival of hypoxic human cortical neurons (derived from induced pluripotent stem cells), monocyte-derived macrophages, and dendritic cells. The results demonstrated that DMT exhibited a significant protective effect via the Sig-1R mediation in severe hypoxia (0.5% O_2). Application of DMT to the media increased the survival rate up to 200%. The positive outcome was linked to the reduced expression and activity of the alpha subunit of the hypoxia-inducible factor 1.

These data suggest that DMT may have a protective impact on both sides of the IRI. This can be achieved by a Sig-1R-dependent mechanism, which helps reduce hypoxic lesions on one hand and has an anti-inflammatory effect on the other.

In vivo studies indicating benefits of DMT administration in IRI of the brain[1]

In a recent animal experiment published in 2020 by our team [59] we studied the effect of DMT on reperfusion injury following artificially induced stroke. Transient occlusion was elicited under general anesthesia by inserting a nylon line into the right middle cerebral artery for 60 minutes. Before the filament removal, one treatment group was administered an intraperitoneal bolus of DMT at a dosage of 1 mg/kg, followed by a continuous maintenance dose of 2 mg/kg/h supplied over 24 hours using osmotic minipumps. Concomitantly with the application of DMT, another group was given the Sig-1R antagonist BD-1063 at a dose of 1 mg/kg as a bolus followed by a maintenance dose of 2 mg/kg/h. Control animals received a bolus of the vehicle only. The volume of the stroke lesions was determined by magnetic resonance imaging 24 hours later. Functional recovery was evaluated using the staircase method in two groups of pre-trained, post-stroke animals—one received DMT and the other received DMT+BD-1063. Animals treated with DMT showed a reduction of lesion volume by almost 50% and their functional recovery improved significantly. The positive effects of DMT were alleviated by the BD-1063 administration. The plasma samples from DMT-treated rats exhibited elevated levels of brain-derived neurotrophic factor and IL-10, whereas the levels of IL1-β, IL-6, and TNF-α were decreased. We concluded that there was a Sig-1R-dependent reduction of post-stroke brain injury following the delivery of exogenous DMT. The presented experimental setup was closer to an anti-reperfusion injury model than to an anti-ischemic one.

Our most recent publication [60] addressed in a different model whether DMT can ameliorate cerebral ischemic injury. Global forebrain ischemia was induced in anesthetized rats by ligation of both common carotid arteries. To increase the metabolic stress, we generated Spreading Depolarizations (SDs) and superimposed a brief (1-minute) period of hypoxia by reducing the amount of oxygen in the anesthetic gas. DMT, PRE-084 (a Sig-1R agonist), NE-100 (a Sig-1R antagonist), and asenapine (a broad-spectrum 5-HT receptor antagonist) were administered intravenously either alone or in combination. The occupation of the cerebral Sig-1Rs by the administered drugs was assessed using a radioligand binding assay. The physiological effect of DMT application was observed by monitoring cerebral blood flow changes with subsequent histopathological workup. Both the Sig-1R agonists, DMT and PRE-084, reduced the extent of SDs, with reduced effectiveness in the presence of the Sig-1R antagonist NE-100. The role of 5-HT receptors was ruled out, as even when they were occupied by asenapine, DMT still could reduce SD amplitude. Overall, DMT decreased neuronal loss and enhanced astrocyte survival in a manner dependent on Sig-1R.

The findings above follow other studies activating Sig1-R by PRE-084 [61] and dexmedetomidine [62] in brain IRI, and indicate, that DMT has the potential to be utilized as an adjuvant treatment for acute cerebral ischemia. Further research should be conducted to explore its possible use in the management of clinical death or neonatal asphyxia.

Since the doses of DMT used in these animal studies were close to the hallucinogenic range (as measured by head-twitching in previous rodent studies)[2], ethical concerns may arise over human applications. Indeed, DMT has significant abuse liability due to its psychedelic effects looked for by substance users. However, its addictive potential and the risk of long-term psychological disturbances are extremely low [63]. The experiences DMT induces typically do not create a strong desire to consume more of the substance [64]. Moreover, the medical emergencies that may benefit from its clinical use involve unconscious subjects or patients under general anesthesia (see below), and DMT has been proven to be safe in alert humans under controlled medical supervision [65,66].

Conclusion

This paper presented indirect support from the literature and direct evidence from our published *in vitro* and *in vivo* studies that DMT may have beneficial therapeutic effects in brain IRI. These data could form a basis for follow-ups by

[1]*These animal experiments were conducted in accordance with the guidelines set by the European Communities Council Directive (86/609 EEC) and the ARRIVE guidelines, with the approval of the Animal Care and Use Committee of the Semmelweis University and University of Szeged, Hungary.*

[2]*The head-twitch response has been widely adopted as a behavioural assay for detecting hallucinogen-like effects.*

human trials and be incorporated into various therapeutic approaches, particularly in the treatment of IRI. Indeed, inspired by the results of our DMT stroke study, Algernon Pharmaceuticals, a Canadian drug development and repurposing company has recently completed a feasibility study and has finalized its clinical trial design for a Phase 2 DMT stroke study. As they announced: "The decision to investigate DMT for stroke treatment was based on the ground-breaking 2020-published rat occlusion stroke study showing that DMT reduced infarct volume and led to an almost full recovery of motor function 30 days after a single treatment with statistical significance." At Algernon, the plan is to investigate whether DMT can be used to treat ischemic stroke to minimize its impact and promote recovery. Current medical methods have limited effectiveness in treating IRI, and there are no effective preventive measures available against reperfusion injury that may develop after thrombolytic therapy of stroke. In the majority of stroke cases, the ischemic phase cannot be predicted, while in surgery the clamping of the arteries is under full control, therefore the anti-hypoxia effect of DMT can be exploited influencing such way both arms of the IRI pathology.

If stroke patients are undergoing general anesthesia during their treatment, the powerful psychedelic effect of DMT should be a minimal concern. Similar reasoning applies to unconscious patients undergoing cardiopulmonary resuscitation within the limited time window under the threat of permanent brain damage. Our global brain hypoxia study offers hope for these cases.

Cardiac arrest is a widespread condition that often leads to a high death rate, even when prompt and well-administered cardiopulmonary resuscitation is performed. While partially successful cardiopulmonary resuscitations may extend one's lifespan, they may not necessarily improve the quality of life during those additional years. Approximately 290,000 cardiac arrests that take place in hospitals are reported annually in the United States. Although this condition is highly prevalent and grave, there are limited options for pharmacological intervention. If DMT can prolong the critical period of clinical death, this could potentially lead to an increased success rate of cardiopulmonary resuscitation and improved long-term functionality. Furthermore, one may also come up with testing DMT or its analogs in perinatal indications against ischemia of the baby's brain with the hope of life saved and made more meaningful. An increased openness concerning optimizing clinical care by the fruits of new research with DMT or its analogs might improve outcomes in broad medical fields.

Our main conclusion is that DMT possesses not only psychedelic properties but also exhibits bioactivity in a broader sense. Its Sig-1R-mediated actions reveal a universal modulatory role in cellular stress-induced changes at the endoplasmic reticulum-mitochondria interface. Our presented arguments do not rely on the conventional understanding of DMT as a hallucinogen that acts on serotonin receptors and produces psychopathological effects. Instead, we intend to shift the focus of research toward its potential role in adaptive somato- and neurophysiological processes.

Funding

Wallace and Indiegogo crowdfunding project, financial support by Bellabeat wellness company.

References

1. Chatterjee PK. Novel pharmacological approaches to the treatment of renal ischemia-reperfusion injury: a comprehensive review. Naunyn Schmiedebergs Arch Pharmacol. 2007 Oct;376(1-2):1-43. doi: 10.1007/s00210-007-0183-5. Epub 2007 Sep 22. PMID: 18038125.
2. Carden DL, Granger DN. Pathophysiology of ischaemia-reperfusion injury. J Pathol. 2000 Feb;190(3):255-66. doi: 10.1002/(SICI)1096-9896(200002)190:3<255::AID-PATH526>3.0.CO;2-6. PMID: 10685060.
3. Eltzschig HK, Eckle T. Ischemia and reperfusion--from mechanism to translation. Nat Med. 2011 Nov 7;17(11):1391-401. doi: 10.1038/nm.2507. PMID: 22064429; PMCID: PMC3886192.
4. Peto K, Nemeth N, Mester A, Magyar Z, Ghanem S, Somogyi V, Tanczos B, Deak A, Bidiga L, Frecska E, Nemes B. Hemorheological and metabolic consequences of renal ischemia-reperfusion and their modulation by N,N-dimethyl-tryptamine on a rat model. Clin Hemorheol Microcirc. 2018;70(1):107-117. doi: 10.3233/CH-170361. PMID: 29660915.
5. Penke B, Fulop L, Szucs M, Frecska E. The Role of Sigma-1 Receptor, an Intracellular Chaperone in Neurodegenerative Diseases. Curr Neuropharmacol. 2018;16(1):97-116. doi: 10.2174/1570159X15666170529104323. PMID: 28554311; PMCID: PMC5771390.
6. Sies H, Berndt C, Jones DP. Oxidative Stress. Annu Rev Biochem. 2017 Jun 20;86:715-748. doi: 10.1146/annurev-biochem-061516-045037. Epub 2017 Apr 24. PMID: 28441057.
7. Kalogeris T, Baines CP, Krenz M, Korthuis RJ. Cell biology of ischemia/reperfusion injury. Int Rev Cell Mol Biol. 2012;298:229-317. doi: 10.1016/B978-0-12-394309-5.00006-7. PMID: 22878108; PMCID: PMC3904795.
8. Mizuma A, Yenari MA. Anti-Inflammatory Targets for the Treatment of Reperfusion Injury in Stroke. Front Neurol. 2017 Sep 7;8:467. doi: 10.3389/fneur.2017.00467. PMID: 28936196; PMCID: PMC5594066.
9. Zuaiter M, Axelrod JH, Pizov G, Gofrit ON. Hyper-Interleukin-6 Protects Against Renal Ischemic-Reperfusion Injury-A Mouse Model. Front Surg. 2021 May 13;8:605675. doi: 10.3389/fsurg.2021.605675. PMID: 34055865; PMCID: PMC8155529.
10. Naito H, Nojima T, Fujisaki N, Tsukahara K, Yamamoto H, Yamada T, Aokage T, Yumoto T, Osako T, Nakao A. Therapeutic strategies for ischemia reperfusion injury in emergency medicine. Acute Med Surg. 2020 Apr 13;7(1):e501. doi: 10.1002/ams2.501. PMID: 32431842; PMCID: PMC7231568.
11. Nemes B, Pető K, Németh N, Mester A, Magyar Z, Ghanem S, Sógor V, Tánczos B, Deák Á, Kállay M, Bidiga L, Frecska E. N,N-dimethyltryptamine Prevents Renal Ischemia-Reperfusion Injury in a Rat Model. Transplant Proc. 2019 May;51(4):1268-1275. doi: 10.1016/j.transproceed.2019.04.005. PMID: 31101212.
12. Sharma N, Patel C, Shenkman M, Kessel A, Ben-Tal N, Lederkremer GZ. The Sigma-1 receptor is an ER-localized type II membrane protein. J Biol Chem. 2021 Nov;297(5):101299. doi: 10.1016/j.jbc.2021.101299. Epub 2021 Oct 11. PMID: 34648767; PMCID: PMC8561001.
13. Hayashi T, Su TP. Sigma-1 receptor chaperones at the ER-mitochondrion interface regulate Ca(2+) signaling and cell survival. Cell. 2007 Nov 2;131(3):596-610. doi: 10.1016/j.cell.2007.08.036. PMID: 17981125.

14. Hayashi T. The Sigma-1 Receptor in Cellular Stress Signaling. Front Neurosci. 2019 Jul 16;13:733. doi: 10.3389/fnins.2019.00733. PMID: 31379486; PMCID: PMC6646578.

15. Delprat B, Crouzier L, Su TP, Maurice T. At the Crossing of ER Stress and MAMs: A Key Role of Sigma-1 Receptor? Adv Exp Med Biol. 2020;1131:699-718. doi: 10.1007/978-3-030-12457-1_28. PMID: 31646531.

16. Zhemkov V, Geva M, Hayden MR, Bezprozvanny I. Sigma-1 Receptor (S1R) Interaction with Cholesterol: Mechanisms of S1R Activation and Its Role in Neurodegenerative Diseases. Int J Mol Sci. 2021 Apr 15;22(8):4082. doi: 10.3390/ijms22084082. PMID: 33920913; PMCID: PMC8071319.

17. Gromek KA, Suchy FP, Meddaugh HR, Wrobel RL, LaPointe LM, Chu UB, Primm JG, Ruoho AE, Senes A, Fox BG. The oligomeric states of the purified sigma-1 receptor are stabilized by ligands. J Biol Chem. 2014 Jul 18;289(29):20333-44. doi: 10.1074/jbc.M113.537993. Epub 2014 May 20. PMID: 24847081; PMCID: PMC4106346.

18. Mishra AK, Mavlyutov T, Singh DR, Biener G, Yang J, Oliver JA, Ruoho A, Raicu V. The sigma-1 receptors are present in monomeric and oligomeric forms in living cells in the presence and absence of ligands. Biochem J. 2015 Mar 1;466(2):263-271. doi: 10.1042/BJ20141321. PMID: 25510962; PMCID: PMC4500508.

19. Chu UB, Ruoho AE. Biochemical Pharmacology of the Sigma-1 Receptor. Mol Pharmacol. 2016 Jan;89(1):142-53. doi: 10.1124/mol.115.101170. Epub 2015 Nov 11. PMID: 26560551.

20. Mori T, Hayashi T, Hayashi E, Su TP. Sigma-1 receptor chaperone at the ER-mitochondrion interface mediates the mitochondrion-ER-nucleus signaling for cellular survival. PLoS One. 2013 Oct 18;8(10):e76941. doi: 10.1371/journal.pone.0076941. PMID: 24204710; PMCID: PMC3799859.

21. Klouz A, Saïd DB, Ferchichi H, Kourda N, Ouanes L, Lakhal M, Tillement JP, Morin D. Protection of cellular and mitochondrial functions against liver ischemia by N-benzyl-N'-(2-hydroxy-3,4-dimethoxybenzyl)-piperazine (BHDP), a sigma1 ligand. Eur J Pharmacol. 2008 Jan 14;578(2-3):292-9. doi: 10.1016/j.ejphar.2007.09.038. Epub 2007 Oct 6. PMID: 17964567.

22. Rizzuto R, Marchi S, Bonora M, Aguiari P, Bononi A, De Stefani D, Giorgi C, Leo S, Rimessi A, Siviero R, Zecchini E, Pinton P. Ca(2+) transfer from the ER to mitochondria: when, how and why. Biochim Biophys Acta. 2009 Nov;1787(11):1342-51. doi: 10.1016/j.bbabio.2009.03.015. Epub 2009 Mar 31. PMID: 19341702; PMCID: PMC2730423.

23. Tagashira H, Zhang C, Lu YM, Hasegawa H, Kanai H, Han F, Fukunaga K. Stimulation of σ1-receptor restores abnormal mitochondrial Ca^{2+} mobilization and ATP production following cardiac hypertrophy. Biochim Biophys Acta. 2013 Apr;1830(4):3082-94. doi: 10.1016/j.bbagen.2012.12.029. Epub 2013 Jan 6. PMID: 23298811.

24. Pal A, Fontanilla D, Gopalakrishnan A, Chae YK, Markley JL, Ruoho AE. The sigma-1 receptor protects against cellular oxidative stress and activates antioxidant response elements. Eur J Pharmacol. 2012 May 5;682(1-3):12-20. doi: 10.1016/j.ejphar.2012.01.030. Epub 2012 Feb 22. PMID: 22381068; PMCID: PMC3314091.

25. Wang J, Shanmugam A, Markand S, Zorrilla E, Ganapathy V, Smith SB. Sigma 1 receptor regulates the oxidative stress response in primary retinal Müller glial cells via NRF2 signaling and system xc(-), the Na(+)-independent glutamate-cystine exchanger. Free Radic Biol Med. 2015 Sep;86:25-36. doi: 10.1016/j.freeradbiomed.2015.04.009. Epub 2015 Apr 25. PMID: 25920363; PMCID: PMC4554890.

26. Su TP, Hayashi T, Maurice T, Buch S, Ruoho AE. The sigma-1 receptor chaperone as an inter-organelle signaling modulator. Trends Pharmacol Sci. 2010 Dec;31(12):557-66. doi: 10.1016/j.tips.2010.08.007. Epub 2010 Oct 1. PMID: 20869780; PMCID: PMC2993063.

27. Su TP, Su TC, Nakamura Y, Tsai SY. The Sigma-1 Receptor as a Pluripotent Modulator in Living Systems. Trends Pharmacol Sci. 2016 Apr;37(4):262-278. doi: 10.1016/j.tips.2016.01.003. Epub 2016 Feb 9. PMID: 26869505; PMCID: PMC4811735.

28. Weng TY, Tsai SA, Su TP. Roles of sigma-1 receptors on mitochondrial functions relevant to neurodegenerative diseases. J Biomed Sci. 2017 Sep 16;24(1):74. doi: 10.1186/s12929-017-0380-6. PMID: 28917260; PMCID: PMC5603014.

29. Couly S, Goguadze N, Yasui Y, Kimura Y, Wang SM, Sharikadze N, Wu HE, Su TP. Knocking Out Sigma-1 Receptors Reveals Diverse Health Problems. Cell Mol Neurobiol. 2022 Apr;42(3):597-620. doi: 10.1007/s10571-020-00983-3. Epub 2020 Oct 23. PMID: 33095392; PMCID: PMC8062587.

30. Fukunaga K. [Orphan receptor and chaperon functions of sigma-1 receptor]. Nihon Yakurigaku Zasshi. 2014 May;143(5):263-4. Japanese. doi: 10.1254/fpj.143.263. PMID: 24813800.

31. Fontanilla D, Johannessen M, Hajipour AR, Cozzi NV, Jackson MB, Ruoho AE. The hallucinogen N,N-dimethyltryptamine (DMT) is an endogenous sigma-1 receptor regulator. Science. 2009 Feb 13;323(5916):934-7. doi: 10.1126/science.1166127. PMID: 19213917; PMCID: PMC2947205.

32. Hayashi T, Su TP. Sigma-1 receptor ligands: potential in the treatment of neuropsychiatric disorders. CNS Drugs. 2004;18(5):269-84. doi: 10.2165/00023210-200418050-00001. PMID: 15089113.

33. Ray TS. Psychedelics and the human receptorome. PLoS One. 2010 Feb 2;5(2):e9019. doi: 10.1371/journal.pone.0009019. Erratum in: PLoS One. 2010;5(3). doi: 10.1371/annotation/e580a864-cf13-40c2-9bd9-b9687a6f0fe4. PMID: 20126400; PMCID: PMC2814854.

34. Hollister LE, Usdin E, Hamburg DA, Barchas JD. Some general thoughts about endogenous psychotogens. Oxford University Press, New York, Neuroregulators and Psychiatric Disorders. 1977; 550-6.

35. Christian ST, Harrison R, Quayle E, Pagel J, Monti J. The in vitro identification of dimethyltryptamine (DMT) in mammalian brain and its characterization as a possible endogenous neuroregulatory agent. Biochem Med. 1977 Oct;18(2):164-83. doi: 10.1016/0006-2944(77)90088-6. PMID: 20877.

36. Barker SA, McIlhenny EH, Strassman R. A critical review of reports of endogenous psychedelic N, N-dimethyltryptamines in humans: 1955-2010. Drug Test Anal. 2012 Jul-Aug;4(7-8):617-35. doi: 10.1002/dta.422. Epub 2012 Feb 28. PMID: 22371425.

37. Jiménez JH, Bouso JC. Significance of mammalian N,N-dimethyltryptamine (DMT): A 60-year-old debate. J Psychopharmacol. 2022 Aug;36(8):905-919. doi: 10.1177/02698811221104054. Epub 2022 Jun 13. PMID: 35695604.

38. Nichols DE. Psychedelics. Pharmacol Rev. 2016 Apr;68(2):264-355. doi: 10.1124/pr.115.011478. Erratum in: Pharmacol Rev. 2016 Apr;68(2):356. PMID: 26841800; PMCID: PMC4813425.

39. Su TP, Hayashi T, Vaupel DB. When the endogenous hallucinogenic trace amine N,N-dimethyltryptamine meets the sigma-1 receptor. Sci Signal. 2009 Mar 10;2(61):pe12. doi: 10.1126/scisignal.261pe12. PMID: 19278957; PMCID: PMC3155724.

40. Wallach JV. Endogenous hallucinogens as ligands of the trace amine receptors: a possible role in sensory perception. Med Hypotheses. 2009 Jan;72(1):91-4. doi: 10.1016/j.mehy.2008.07.052. Epub 2008 Sep 20. PMID: 18805646.

41. Dean JG, Liu T, Huff S, Sheler B, Barker SA, Strassman RJ, Wang MM, Borjigin J. Biosynthesis and Extracellular Concentrations of N,N-dimethyltryptamine (DMT) in Mammalian Brain. Sci Rep. 2019 Jun 27;9(1):9333. doi: 10.1038/s41598-019-45812-w. PMID: 31249368; PMCID: PMC6597727.

42. Frecska E, Szabo A, Winkelman MJ, Luna LE, McKenna DJ. A possibly sigma-1 receptor mediated role of dimethyltryptamine in tissue protection, regeneration, and immunity. J Neural Transm (Vienna). 2013 Sep;120(9):1295-303. doi: 10.1007/s00702-013-1024-y. Epub 2013 Apr 26. PMID: 23619992.

43. Mondello C, Micali A, Baldino G, Cardia L, Alibrandi A, Asmundo A, Sapienza D, Puzzolo D, Ventura Spagnolo E. "Immunohistochemical analysis of Sigma-1 receptor (σ-1R) expression in human pineal gland

in relation to different causes of death". Leg Med (Tokyo). 2024 Mar 7;69:102434. doi: 10.1016/j.legalmed.2024.102434. Epub ahead of print. PMID: 38493555.

44. Mavlyutov TA, Epstein ML, Liu P, Verbny YI, Ziskind-Conhaim L, Ruoho AE. Development of the sigma-1 receptor in C-terminals of motoneurons and colocalization with the N,N'-dimethyltryptamine forming enzyme, indole-N-methyl transferase. Neuroscience. 2012 Mar 29;206:60-8. doi: 10.1016/j.neuroscience.2011.12.040. Epub 2012 Jan 4. PMID: 22265729; PMCID: PMC3321351.

45. Ruoho AE, Chu UB, Ramachandran S, Fontanilla D, Mavlyutov T, Hajipour AR. The ligand binding region of the sigma-1 receptor: studies utilizing photoaffinity probes, sphingosine and N-alkylamines. Curr Pharm Des. 2012;18(7):920-9. doi: 10.2174/138161212799436584. PMID: 22288412; PMCID: PMC4440231.

46. Omi T, Tanimukai H, Kanayama D, Sakagami Y, Tagami S, Okochi M, Morihara T, Sato M, Yanagida K, Kitasyoji A, Hara H, Imaizumi K, Maurice T, Chevallier N, Marchal S, Takeda M, Kudo T. Fluvoxamine alleviates ER stress via induction of Sigma-1 receptor. Cell Death Dis. 2014 Jul 17;5(7):e1332. doi: 10.1038/cddis.2014.301. PMID: 25032855; PMCID: PMC4123092.

47. Jarrott B, Williams SJ. Chronic Brain Inflammation: The Neurochemical Basis for Drugs to Reduce Inflammation. Neurochem Res. 2016 Mar;41(3):523-33. doi: 10.1007/s11064-015-1661-7. Epub 2015 Jul 16. PMID: 26177578.

48. Gao QJ, Yang B, Chen J, Shi SB, Yang HJ, Liu X. Sigma-1 Receptor Stimulation with PRE-084 Ameliorates Myocardial Ischemia-Reperfusion Injury in Rats. Chin Med J (Engl). 2018 Mar 5;131(5):539-543. doi: 10.4103/0366-6999.226076. PMID: 29483387; PMCID: PMC5850669.

49. Lachance V, Bélanger SM, Hay C, Le Corvec V, Banouvong V, Lapalme M, Tarmoun K, Beaucaire G, Lussier MP, Kourrich S. Overview of Sigma-1R Subcellular Specific Biological Functions and Role in Neuroprotection. Int J Mol Sci. 2023 Jan 19;24(3):1971. doi: 10.3390/ijms24031971. PMID: 36768299; PMCID: PMC9916267.

50. Lin CY, Wu HE, Weng EF, Wu HC, Su TP, Wang SM. Fluvoxamine Exerts Sigma-1R to Rescue Autophagy via Pom121-Mediated Nucleocytoplasmic Transport of TFEB. Mol Neurobiol. 2024 Jan 5. doi: 10.1007/s12035-023-03885-9. Epub ahead of print. PMID: 38180612.

51. Prasanth MI, Malar DS, Tencomnao T, Brimson JM. The emerging role of the sigma-1 receptor in autophagy: hand-in-hand targets for the treatment of Alzheimer's. Expert Opin Ther Targets. 2021 May;25(5):401-414. doi: 10.1080/14728222.2021.1939681. Epub 2021 Jun 17. PMID: 34110944.

52. Yang S, Bhardwaj A, Cheng J, Alkayed NJ, Hurn PD, Kirsch JR. Sigma receptor agonists provide neuroprotection in vitro by preserving bcl-2. Anesth Analg. 2007 May;104(5):1179-84, tables of contents. doi: 10.1213/01.ane.0000260267.71185.73. PMID: 17456670; PMCID: PMC2596726.

53. Zhang Y, Shi Y, Qiao L, Sun Y, Ding W, Zhang H, Li N, Chen D. Sigma-1 receptor agonists provide neuroprotection against gp120 via a change in bcl-2 expression in mouse neuronal cultures. Brain Res. 2012 Jan 11;1431:13-22. doi: 10.1016/j.brainres.2011.10.053. Epub 2011 Nov 6. PMID: 22133307.

54. Ruscher K, Wieloch T. The involvement of the sigma-1 receptor in neurodegeneration and neurorestoration. J Pharmacol Sci. 2015 Jan;127(1):30-5. doi: 10.1016/j.jphs.2014.11.011. Epub 2014 Dec 9. PMID: 25704015.

55. Dakic V, Minardi Nascimento J, Costa Sartore R, Maciel RM, de Araujo DB, Ribeiro S, Martins-de-Souza D, Rehen SK. Short term changes in the proteome of human cerebral organoids induced by 5-MeO-DMT. Sci Rep. 2017 Oct 9;7(1):12863. doi: 10.1038/s41598-017-12779-5. PMID: 28993683; PMCID: PMC5634411.

56. Kelley DP, Venable K, Destouni A, Billac G, Ebenezer P, Stadler K, Nichols C, Barker S, Francis J. Pharmahuasca and DMT Rescue ROS Production and Differentially Expressed Genes Observed after Predator and Psychosocial Stress: Relevance to Human PTSD. ACS Chem Neurosci. 2022 Jan 19;13(2):257-274. doi: 10.1021/acschemneuro.1c00660. Epub 2022 Jan 6. PMID: 34990116.

57. Szabo A, Kovacs A, Frecska E, Rajnavolgyi E. Psychedelic N,N-dimethyltryptamine and 5-methoxy-N,N-dimethyltryptamine modulate innate and adaptive inflammatory responses through the sigma-1 receptor of human monocyte-derived dendritic cells. PLoS One. 2014 Aug 29;9(8):e106533. doi: 10.1371/journal.pone.0106533. PMID: 25171370; PMCID: PMC4149582.

58. Szabo A, Kovacs A, Riba J, Djurovic S, Rajnavolgyi E, Frecska E. The Endogenous Hallucinogen and Trace Amine N,N-Dimethyltryptamine (DMT) Displays Potent Protective Effects against Hypoxia via Sigma-1 Receptor Activation in Human Primary iPSC-Derived Cortical Neurons and Microglia-Like Immune Cells. Front Neurosci. 2016 Sep 14;10:423. doi: 10.3389/fnins.2016.00423. PMID: 27683542; PMCID: PMC5021697.

59. Nardai S, László M, Szabó A, Alpár A, Hanics J, Zahola P, Merkely B, Frecska E, Nagy Z. N,N-dimethyltryptamine reduces infarct size and improves functional recovery following transient focal brain ischemia in rats. Exp Neurol. 2020 May;327:113245. doi: 10.1016/j.expneurol.2020.113245. Epub 2020 Feb 14. PMID: 32067950.

60. Szabó Í, Varga VÉ, Dvorácskó S, Farkas AE, Körmöczi T, Berkecz R, Kecskés S, Menyhárt Á, Frank R, Hantosi D, Cozzi NV, Frecska E, Tömböly C, Krizbai IA, Bari F, Farkas E. N,N-Dimethyltryptamine attenuates spreading depolarization and restrains neurodegeneration by sigma-1 receptor activation in the ischemic rat brain. Neuropharmacology. 2021 Jul 1;192:108612. doi: 10.1016/j.neuropharm.2021.108612. Epub 2021 May 21. PMID: 34023338.

61. Zhao X, Zhu L, Liu D, Chi T, Ji X, Liu P, Yang X, Tian X, Zou L. Sigma-1 receptor protects against endoplasmic reticulum stress-mediated apoptosis in mice with cerebral ischemia/reperfusion injury. Apoptosis. 2019 Feb;24(1-2):157-167. doi: 10.1007/s10495-018-1495-2. PMID: 30387007.

62. Zhao Q, Yu S, Ling Y, Hao S, Liu J. The Protective Effects of Dexmedetomidine against Hypoxia/Reoxygenation-Induced Inflammatory Injury and Permeability in Brain Endothelial Cells Mediated by Sigma-1 Receptor. ACS Chem Neurosci. 2021 Jun 2;12(11):1940-1947. doi: 10.1021/acschemneuro.1c00032. Epub 2021 May 20. PMID: 34014076.

63. Gable RS. Risk assessment of ritual use of oral dimethyltryptamine (DMT) and harmala alkaloids. Addiction. 2007 Jan;102(1):24-34. doi: 10.1111/j.1360-0443.2006.01652.x. PMID: 17207120.

64. Winstock AR, Kaar S, Borschmann R. Dimethyltryptamine (DMT): prevalence, user characteristics and abuse liability in a large global sample. J Psychopharmacol. 2014 Jan;28(1):49-54. doi: 10.1177/0269881113513852. Epub 2013 Nov 27. PMID: 24284475.

65. Strassman RJ, Qualls CR. Dose-response study of N,N-dimethyltryptamine in humans. I. Neuroendocrine, autonomic, and cardiovascular effects. Arch Gen Psychiatry. 1994 Feb;51(2):85-97. doi: 10.1001/archpsyc.1994.03950020009001. PMID: 8297216.

66. Strassman RJ, Qualls CR, Uhlenhuth EH, Kellner R. Dose-response study of N,N-dimethyltryptamine in humans. II. Subjective effects and preliminary results of a new rating scale. Arch Gen Psychiatry. 1994 Feb;51(2):98-108. doi: 10.1001/archpsyc.1994.03950020022002. PMID: 8297217.